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13. ABSTRACT ***(Maximum 200 Words)***

We propose a training grant to recruit and train two postdoctoral students and three physicians. These trainees will acquire skills in the epidemiology and prevention of breast cancer. They will work closely with mentors who have a long track record of training epidemiologists. The funding will allow our research group to focus specific training opportunities on breast cancer. The ongoing epidemiologic studies and prevention trials offer a unique resource in which trainees can participate in cutting edge research and acquire skills that will establish them as future leaders. We have to date enrolled two postdoctoral fellows, Heather Baer and Heather Eliassen, entering the second year of training; an MD trainee, Ann Partridge, completed her first year of training and received her MPH and is now entering into the second year where she will work in research. We also have a second MD, Larissa Nekhlyadov, to begin the first year of training and we are still in the process of recruiting a third MD. We established the Advanced Cancer Epidemiology Seminar in Breast Cancer in which all trainees participated. The seminar met once per week for eight weeks this past spring and will continue again this coming spring.

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INTRODUCTION

We have proposed a training grant to recruit and train two doctoral students and three physicians. These trainees will acquire skills in the epidemiology and prevention of breast cancer. They will work closely with mentors who have a long track record of training epidemiologists. The funding will allow our research group to focus specific training opportunities on breast cancer. The ongoing epidemiologic studies and prevention trials offer a unique resource in which trainees can participate in cutting edge research and acquire skills that will establish that will establish them as future leaders.

BODY

(Approved Statement of Work is italicized)

We will advertise and recruit ***one pre-doctoral candidate*** *for the first year of this proposed training program.* We did not recruit in the first year (year one was expected to begin 7/1/00) due to funding not being received until September 2000 we were delayed in starting the recruitment process.

We will advertise and recruit ***one physician for a two-year training*** *opportunity that includes course work in the first year and research on one of the ongoing studies in the second year.* We have recruited Dr. Ann Partridge, MD whose research focuses on the assessment, perception and communication of breast cancer risk as well as other aspects of provider-patient communication in oncology. Other projects she is involved in include breast cancer prevention and adherence with oral antineoplastic agents. In the first year of the grant, she was involved in starting a breast cancer chemoprevention study in conjunction with the Cancer Risk and Prevention Clinic at Dana-Farber and the Nurses' Health Study. This study, a randomized placebo controlled trial, will assess the safety and feasibility of utilizing an aromatase inhibitor for breast cancer prevention in women who are at high risk for breast cancer based on an elevated estradiol level. In March 2002 she received her MPH from Harvard School of Public Health and this year she will continue working in the second year of the breast cancer chemoprevention study in conjunction with the Cancer Risk and Prevention Clinic at Dana-Farber Cancer Institute and the Nurses' Health Study. This study, a randomized placebo-controlled trial, is assessing the safety and feasibility of utilizing an aromatase inhibitor for breast cancer prevention in women who are at high risk for breast cancer based on an elevated estradiol level. She also developed a research plan to study adherence with oral antineoplastic agents. She published a review on this subject in the Journal of the National Cancer Institute[1] and recently submitted a manuscript evaluating non-adherence with adjuvant tamoxifen in patients with early stage breast cancer in a large population.[2] As part a planned NIH Career Development Award application, she plans to evaluate the relationship between non-adherence and survival in this same database. In conjunction with this, she plans to study adherence with oral antineoplastic agents in breast cancer patients in several breast cancer clinics to better understand adherence from a biopsychosocial perspective. Dr. Partridge is also currently piloting questionnaires among breast cancer patients on oral investigational agents in her clinic. In addition, in the past year, she was selected as Adherence Co-Chair of a large national NIH-funded randomized study conducted by CALGB comparing oral chemotherapy to standard chemotherapy in older breast cancer patients. She will be measuring adherence among a subset of patients on the oral medication in association with reported side effects, quality of life, health beliefs, and other variables.

Another research plan she is pursuing entails understanding the issues surrounding sharing clinical trial results with participants. She recently published a commentary on this subject in the Journal of the American Medical Association[3] and she presented an abstract at this year's ASCO describing a study she performed on patient preferences and attitudes about this issue.[4] This manuscript is in preparation. She is currently conducting a national survey of over 2000 oncology physicians and nurses through the CALGB evaluating their attitudes about this issue. This study is funded by an ASCO Young Investigator's Award and results will be presented at next year's ASCO.

Her other ongoing projects include a study assessing risk perceptions of women with DCIS as well as assessing physician perceptions of DCIS risk as part of the Dana-Farber breast cancer SPORE, and she is co-investigator on an R-01 to evaluate and improve risk communication among women with DCIS and early stage breast cancer. These are examples of the training opportunities that this award has afforded us.

We will recruit ***a second pre-doctoral candidate*** *to begin training in the second year. During the second year we will advertise for* ***two physicians*** *to begin training in the third year.* We have recruited two pre-doctoral students, Heather Baer and Heather Eliassen, to make up for the first year. Both have completed the first year of training which involved course work, including advanced epidemiologic methods, cancer cell biology, biostatistics, nutritional epidemiology, research synthesis and the use of biomarkers in epidemiology. Ms. Baer and Ms. Eliassen also successfully passed the departmental qualifying exam. This is a significant step towards attaining a doctorate degree. This summer Ms. Eliassen will be working on

data analysis in the Nurses' Health Study, exploring possible dissertation topics such as adult weight loss and breast cancer risk and tubal ligation and breast cancer risk.

Ms. Baer has begun to develop her own research in the field of breast cancer etiology and prevention. Areas of interest are early life and adolescent risk factors for breast cancer, predictors of benign breast disease and conditions associated with future breast cancer risk. She has submitted a manuscript on Adolescent Diet and Benign Breast Disease utilizing the resources of the Nurses' Health Study II. This will be presented at the Era of Hope DOD Breast Cancer Research Program Meeting in September 2002. She will also begin her doctoral thesis this year. These are also great examples of the training opportunities that this award has afforded our group.

This past year we have been actively recruiting for the two physician's slots to begin this year. We have one physician beginning this summer, Dr. Larissa Nekhlyadov, and we continue to search for the second physician trainee.

During the first ***year we will develop and implement an advanced seminar in breast cancer.*** *This will bring new depth to course work not previously available at the Harvard School of Public Health. This seminar will cover topics in detail and will span from basic biology of the breast, to early lesions, epidemiologic risk factors, statistical models of breast cancer incidence and issues in risk stratification and counseling for prevention.* The Breast Cancer Program of Dana Farber/Harvard Cancer Center has run a monthly seminar in unsolved research issues for breast cancer. Last year this seminar was attended by the first physician trainee, Ann Partridge. This past spring, an eight-week seminar was developed and implemented specifically for breast cancer epidemiology, covering such topics as modeling breast cancer risk, postmenopausal hormones and breast cancer, gene environment interactions and benign breast disease. It was attended by Heather Baer, Heather Eliassen and Dr. Partridge along with other breast cancer researchers. It is planning to resume again for spring 2003.

KEY RESEARCH ACCOMPLISHMENTS IN REFERENCE TO STATEMETN OF WORK

- We have successfully recruited two pre-doctoral fellows. They both have completed required coursework with commendation and passed the departmental exam progressing towards the doctorate degree. They both continue with analyses this summer utilizing the training opportunities in the Nurses' Health Study group and will continue coursework in the fall and a dissertation.
- We have successfully recruited two post-doctoral, physician trainees. The first Dr. Ann Partridge received her MPH this past March is entering into her second year of training in many research projects exemplifying the training opportunities this award has afforded our group. Our second recruit, Dr. Larissa Nekhlyodov is beginning now.
- We have had all our trainees form the past year attend the eight week Advanced Cancer Epidemiology Seminar in Breast Cancer which will resume this coming spring.

REPORTABLE OUTCOMES

- Dr. Ann Partridge now has four peer reviewed journal articles; three of which she is first author and involve clinical and epidemiologic issues. See appendices 1-4. Last year she presented the attached abstract at the American Society of clinical Oncology. See appendix 5.
- Heather Baer has written an abstract which will be presented at the Era of Hope DOD Breast Cancer Research Program Meeting. See appendix 6.
- Dr. Ann Partridge was awarded her MPH from Harvard School of Public Health.
- Both predoctoral trainees, Heather Eliassen and Heather Baer passed the Harvard School of Public Health's epidemiology departmental exam.

CONCLUSIONS

Our trainees in breast cancer epidemiology and prevention are proving to be exceptional researchers. As a result of this award, trainees graduate with advanced degrees in epidemiology from HSPH and the resources of the on-going epidemiologic research at the Brigham and Women's Hospital are providing excellent training opportunities for more in depth breast cancer epidemiology and prevention. As we progress, we are achieving our goals of training professionals in translational research. We are still in the process of recruiting one more physician and have had interest but none completely eligible due to citizenship requirements.

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APPENDICES

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Quality of Life Issues Among Women Undergoing High-Dose Chemotherapy for Breast Cancer

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ABSTRACT: High-dose chemotherapy with autologous stem cell support for the treatment of breast cancer can have a profound effect on patients' quality of life (QOL). This article reviews findings from studies assessing QOL before, during, and after high-dose chemotherapy. The impact of high-dose therapy on overall QOL and specific aspects of QOL including physical functioning, symptoms, psychosocial/emotional and cognitive functioning, sexual functioning, and role functioning is considered. High-dose chemotherapy with stem cell transplant results in largely transient impairment of overall QOL and physical functioning, with subsequent improvement to baseline or better over time. Despite these encouraging global QOL findings, many patients continue to suffer considerable symptoms and concerns attributable to their transplant long after completion of the therapy. Additional research in this area is needed to optimize QOL for patients receiving high-dose chemotherapy.

INTRODUCTION

The role of high-dose chemotherapy with autologous bone marrow or peripheral stem cell support (autologous bone marrow transplant) for women with breast cancer has been controversial. To date, randomized trials of high-dose chemotherapy in women with metastatic disease or high-risk primary breast cancer have revealed no apparent benefit over standard therapy [1–7]. However, because of short follow-up times, small sample sizes, and heterogeneous trial designs, the utility of high-dose chemotherapy remains a question for study in the context of well-designed clinical trials [8]. In evaluating the use of high-dose chemotherapy for breast cancer, one aspect that has received increasing attention has been the impact of treatment on quality of life (QOL). Over the past decade, interest has grown in the assessment of QOL both during and after cancer treatment, including transplant [9–11]. Because QOL information can provide a broader understanding of patients' treatment experiences beyond the traditional endpoints of survival, disease free survival, and time-to-progression, it has the potential to become another index of the 'effectiveness' of treatments [9,12]. In fact, the Food and Drug Administration (FDA) in recent years has linked new drug approval to improvement in survival *or* quality of life [13].

QOL assessment, particularly in phase III studies, can provide important information about the risks and benefits of treatment programs. Measuring QOL in randomized trials is particularly useful in two situations: 1) when there are substantial differences in toxicity across the treatment arms; or 2) when a significant survival difference between treatment arms is unlikely [14]. Currently, these tenets appear to be true for high-dose chemotherapy in comparison to standard treatment for breast cancer. High-dose chemotherapy is associated with significantly increased acute morbidity compared to standard dose regimens and, thus far, results in no demonstrable improvement in survival. For these reasons, assessment of QOL is particularly important in evaluating this treatment.Traditionally, clinicians have used antitumor activity, perform-

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Appendix 1

ance status, and standard toxicity measures (e.g., nausea, myelosuppression, and asthenia) as surrogates for QOL associated with specific cancer therapy [15]. However, the effects of disease and treatment on QOL are more complicated than these traditional surrogates allow. QOL can be conceptualized as a multidimensional construct encompassing a variety of distinct domains [16–18]. Table 1 lists the specific factors that contribute to overall QOL.

Several instruments have been developed and validated to assess overall QOL in cancer patients. Some of these instruments focus more specifically on women with breast cancer [14,19]. Still, there is no single instrument that is considered the "gold standard" for QOL assessment in patients with breast cancer. Investigators have used a variety of different measures in evaluating QOL, which contributes to the difficulty comparing QOL outcomes across studies. Furthermore, there have been relatively few randomized trials of high-dose chemotherapy versus standard therapy for patients with breast cancer, and even fewer that have incorporated any formal QOL assessment. Nevertheless, existing data obtained from studies in patients with breast cancer, as well as findings in patients undergoing transplant as treatment for other malignancies, provide insight into QOL experienced by women receiving high-dose therapy.

Table 2 lists selected studies assessing overall QOL and its various dimensions among patients with breast cancer undergoing high-dose chemotherapy with stem cell support. The studies vary extensively with regard to number of subjects, type of study (phase I/II/randomized III), instruments used, and mode or timing of assessment.

OVERALL QOL AND PHYSICAL FUNCTIONING

Several investigators have addressed the overall QOL of women undergoing high- dose chemotherapy for breast cancer. Most published series document positive patient satisfaction levels with overall QOL following high-dose therapy. In some instances, patients have reported better QOL scores following high-dose therapy than preceding the procedure [20–22]. It must be recognized, however, that prior to treatment many women were receiving standard chemotherapy or adjusting to a new diagnosis of breast cancer. For example, McQuellon et al. found that QOL in women who were disease free following high-dose therapy was better than they had reported prior to therapy [20]. Only women free of recurrent disease were included in this study. Not unexpectedly, current disease status appears to be a powerful determinant of QOL. In a study by Winer and colleagues, Functional Living Index-Cancer (FLIC) scores were significantly lower in women with evidence of recurrent disease following transplant than in patients who were free of disease at the time of the evaluation [21].

Longitudinal studies assessing QOL in patients receiving high-dose therapy reveal a predictable pattern of change over time. In a study of 86 patients assessed prior to and following transplant (37% for breast cancer), McQuellon and colleagues found that overall QOL scores were parabolic, with overall QOL worsening at discharge, then improving at 100 days and at one

Table 1
Quality of Life Domains

Physical functioning (Performance Status)
Psychological/Emotional functioning
Symptoms
Social Interactions
Sexuality
Vocational Status
Satisfaction with Health Care

Table 2
Studies assessing QOL in breast cancer patients undergoing high-dose chemotherapy with stem cell transplant

Authors	Study Design	Timing of assessments	N	Measures of assessments
Peters et al. [30]	Cross-sectional	Post-transplant	43	FLIC, SDS
McQuellon et al. [20]	Longitudinal	Pre-, Post-transplant	52	FACT-BMT, POMS-TMDS, MOS-SSS, CES-D, interviewer questionnaire,WHO PS
Larsen et al. [24]	Longitudinal	Pre-, Post-transplant	9	SIP, SWED-QUAL
Hann et al. [12]	Cross-sectional	Post-transplant	43	SF-36, PSR, MSAS
McQuellon et al. [22]	Longitudinal	Pre-, Post-transplant serially	86 (37% breast ca)	FACT-BMT, POMS-TMDS, MOS-SSS, CES-D, inter-viewer questionnaire, PSR
Andrykowski et al. [31]	Cross-sectional	Post-transplant	110 (60% breast ca)	Demographic information form, SCQ, WHO PS
Hann et al. [23]	Longitudinal	During transplant	31	POMS-F, FSI, STAI, CES-D
Winer et al. [21]	Cross-sectional	Post-transplant	82	FLIC, SDS, sexual function survey
Macquart-Moulin et al. [25]	Longitudinal	Pre, Post-transplant, serially	95 (76% breast ca)	EORTC QLQ-C30, side-effect questionnaire
Randomized studies				
ten Vergert et al. [27]	Longitudinal	Pre-, Post-transplant serially	225	SF-36, RSCL
Winer et al. [28]	Longitudinal	Pre-, Post-transplant serially	210	FLIC, SDS, PAIS
Forbes et al. [26]	Longitudinal	Pre-, post-transplant serially	166	EORTC QLQ-C30

Abbreviations: FLIC, Functional Living Index-Cancer; SDS, Symptom Distress Scale; FACT-BMT, Functional Assessment of Cancer Therapy Bone Marrow Transplant; POMS-TMDS, Profile of Mood States Total Mood Disturbance Scale; MOS-SSS, Medical Outcome Study-Social Support Survey; CES-D, Center for Epidemiological Studies-Depression Scale Screener; WHO PS, World Health Organization Performance Status Rating/Scale; SIP, Sickness Impact Profile; SWED-QUAL, Swedish Health-Related Quality of Life Questionnaire; SF-36, Medical Outcome Study-Short Form-36; PSR, Performance Status Rating Scale; MSAS, Memorial Symptom Assessment Scale; SCQ, Stem Cell Transplant Concerns Questionnaire; POMS-F, Profile of Mood States Fatigue Scale; FSI, Fatigue Symptom Inventory; STAI, State-Trait Anxiety Inventory; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; RSCL, Rotterdam Symptom Check List; PAIS, Psychosocial Adjustment to Illness Scale.

year following discharge [22]. Although specific deficits (e.g., fatigue) remained at one year, mean overall QOL scores were improved from baseline. Hann et al. found, not unexpectedly, that despite similar baseline values, women undergoing transplant had significantly increased frequency and severity of fatigue compared to women without cancer [23]. Furthermore, women undergoing transplant reported significantly worse depressive symptomatology at the end of active treatment as compared to healthy subjects. There was no statistically significant difference in reported anxiety between transplant patients and healthy subjects; although patients undergoing transplant did experience increased anxiety midtreatment, this largely returned to baseline by the completion of therapy.

The early detrimental effects of transplant appear to be short-lived in most individuals. Larsen et al. found that functional capacity and QOL were worse at hospital discharge than at either baseline or 7–15 weeks post-transplant [24]. Macquart-Moulin et al. confirmed these findings in a French multicenter trial of the treatment of inflammatory breast cancer [25]. During high-dose therapy, the frequency of symptoms was high and QOL was impaired, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30). QOL improved significantly after completion of treatment with some persistence of difficulties in the area of physical functioning. One year after initiation of therapy, most scores had returned to baseline with both emotional functioning and global QOL scores reportedly better than baseline.

The randomized studies that have included formal QOL evaluation have also revealed this overall pattern of early deficits during or immediately after transplant, followed by near complete recovery to baseline or better [26–28]. Forbes and colleagues assessed overall QOL in the Anglo-Celtic randomized trial of high-dose adjuvant chemotherapy [26]. Using the QLQ-C30, no significant differences were observed at six months and one year after randomization between the 82 women who had received conventional chemotherapy and the 84 women who had received high-dose chemotherapy with stem cell support. At six months, both regimens had resulted in significant deterioration in QOL. However, after one year, QOL had returned to baseline for both groups. Analysis of the QLQ-C30 sub-scales revealed that, in the short term, high-dose therapy had a greater impact on everyday social functioning that resolved by one year. Both groups of women were found to be significantly less tense and worried at six months and one year than at randomization (baseline). In another randomized study of standard versus high-dose chemotherapy as adjuvant therapy for women with breast cancer, women receiving high-dose therapy had lower Medical Outcome Study-Short Form-36 (SF-36) scores and decreased physical activity scores early after therapy when compared to women receiving standard therapy [27]. However, re-evaluation six months following therapy revealed no significant differences between the two groups and, at one year, scores for both groups were not significantly different from healthy women.

Winer et al. conducted longitudinal QOL assessments as a companion study to Cancer and Leukemia Group B (CALGB) trial 9082, which randomized women with ≥ 10 nodes positive to high-dose chemotherapy with stem cell support or intermediate dose chemotherapy [28,29]. Using the FLIC, Symptom Distress Scale (SDS), and the Psychological Adjustment to Illness Scale (PAIS), QOL was measured for 210 patients at baseline, 3 months, 1 year, 2 years, and 3 years following treatment. Although QOL scores were similar at baseline, women randomized to high-dose chemotherapy demonstrated inferior scores on overall QOL, symptoms, and social functioning at 3 months post-treatment. QOL as measured by FLIC scores improved with time in both arms, with FLIC scores nearly identical in the two groups at 1, 2, and 3 years.

Thus, it appears that high-dose chemotherapy with stem cell transplant results in largely transient decreases in overall QOL and physical functioning with subsequent improvement to baseline or better over time. These results are reassuring. Although short-term impairment should be considered, long-term QOL is likely to be more

important in determining the overall value of high-dose chemotherapy in women with breast cancer.

Despite these encouraging global QOL findings, many patients continue to suffer considerable symptoms attributable to their transplant long after completion of the therapy. Peters and colleagues assessed QOL and symptoms using the Functional Living Index-Cancer (FLIC) and Symptom Distress Scale (SDS) among women more than one year after high-dose chemotherapy with autologous transplant for high-risk breast cancer [30]. Although overall QOL as assessed by the FLIC was quite favorable, women reported moderate to severe difficulty with a number of symptoms including difficulty sleeping (43%), fatigue (27%), and worry (25%). Despite an overall QOL improvement from pre-transplant baseline in the study by McQuellon and colleagues, 30% of patients complained of problems with sexuality, fatigue, and depression an average of nine months following transplant [20]. These findings were corroborated in a second study by the same authors in 86 patients (37% with breast cancer) who had undergone either autologous or allogeneic transplant [22]. Hann et al. compared women with no cancer history to 43 women who were an average of 3.3 years post-transplant [12]. Using the SF-36, Performance Status Rating Scale (PSR), and Memorial Symptom Assessment Scale (MSAS), they found significantly impaired physical functioning, general health, vitality, physical role functioning, social functioning, and emotional role functioning among women who had undergone high-dose chemotherapy, even when assessed at a range of 1–8 years following transplant. Furthermore, impaired QOL following transplant was associated with lower income, longer time to engraftment, longer hospital stay, poor performance status, and greater symptom prevalence, severity, and distress [12].

Winer and colleagues assessed QOL in patients surviving at least 12 months after high-dose chemotherapy with stem cell support [21]. Written questionnaires and follow-up telephone interviews were conducted a median of 30.6 months after transplant. Eighty-two patients completed the FLIC, SDS, and a survey of sexual function developed by the authors. Commonly reported symptoms included insomnia, fatigue, and pain. Interestingly, no significant association was seen between overall QOL as measured by the FLIC and either age or the time elapsed since transplant. FLIC scores were significantly lower in patients with evidence of recurrent disease at the time of evaluation and in patients who described themselves as staying at home compared with patients who were either employed or looking for work. Women with active metastatic disease at the time of assessment were more likely to report severe symptoms on the Symptom Distress Scale.

In their assessment of symptoms, psychological adjustment and QOL as part of a randomized trial of high-dose chemotherapy, Winer and colleagues in the CALGB found similar results [28]. Although scores were similar at baseline, women randomized to high-dose chemotherapy demonstrated more severe symptoms and inferior social functioning at three months post-treatment compared to women randomized to intermediate dose chemotherapy. The most commonly reported symptoms (moderate or severe) three months after treatment with high-dose chemotherapy were fatigue, insomnia, difficulty with outlook, concern about appearance, and problems with appetite and concentration. By one year after treatment, most symptoms had improved, and there were few differences between women randomized to high versus intermediate dose therapy. However, moderate to severe fatigue, insomnia, difficulty with outlook, and concern with appearance were cited by 15–30% of the patients.

PSYCHOSOCIAL, EMOTIONAL, AND COGNITIVE FUNCTIONING

There is considerable psychosocial morbidity among women undergoing transplant, even prior to the treatment, when compared with normal subjects [19]. Such baseline difficulties may account for the improvement in overall QOL, and its individual dimensions, following transplant

observed in several studies. Ten Vergert et al. found a reduction in complaints of stress, as assessed by the Rotterdam Symptom Checklist (RSCL), both during and following completion of therapy among women receiving either high-dose chemotherapy or standard chemotherapy [27]. In a randomized trial comparing high-dose adjuvant chemotherapy with standard chemotherapy, Forbes et al. found that both groups were significantly less tense and worried at six months and one year than at the time of randomization [26].

Some transplant patients continue to suffer emotional distress and concerns following transplant, even after a considerable length of time. Although McQuellon et al. found that the global trajectory for distress among transplant patients was linear and improved with time, approximately 20% of patients continued to have psychological distress at one year [22]. Furthermore, patient concerns increased over time, even as self-reported physical well-being and distress improved. In their evaluation of women with stage II–IV breast cancer undergoing transplant, McQuellon et al. found that QOL and mood following transplant improved slightly from baseline [20]. However, a third of the patients reported depressive symptoms up to two years following transplant. In addition, several patients expressed residual concerns in multiple other areas including: job or work situation (25%); finances (42%); general physical health (50%); general frame of mind (25%); appearance (33%); health or life insurance (37%); personal or intimate physical relations (33%); and planning for the future (38%). Only one patient reported regretting the transplant 'a little', while the 23 other patients undergoing post-transplant evaluation had no regrets about undergoing the transplant treatment.

Andrykowski and colleagues explored psychosocial concerns among 110 patients (66 with breast cancer) a mean of 17 months post transplant (87% autologous) [31]. Patients were concerned about the possibility of recurrent disease (95% of respondents), energy level (91%), and whether they would 'return to normal' (79%). Many also reported feeling depressed, tense or anxious (74%). Other common areas of concern included personal appearance (71%), difficulties with memory and concentration (67%), sexuality (67%), poor appetite (63%), and poor sleep (63%). In the group as a whole, patients who were younger, female, and had a poorer performance status reported a larger number of concerns post-transplant. Concerns about recurrent disease, 'returning to normal', and energy level appeared important throughout the post-transplant course. Patients who were early in recovery were more concerned about the quality of their medical care and overprotectiveness of others, whereas concerns about anxiety, sexual function, sleep, intimate relationships, and ability to be affectionate were more important to patients who were further from transplant.

In women with breast cancer, impaired QOL is not confined to the transplant setting. Other intensive treatments have been shown to be associated with decreased QOL. Dose-dense adjuvant chemotherapy regimens have resulted in increased, though transient, psychological distress in comparison to standard therapy. Del Mastro and colleagues evaluated psychological effects in women with early stage breast cancer randomized to standard chemotherapy compared to dose-dense chemotherapy requiring G-CSF support [32]. Psychological distress was measured using the Psychological Distress Inventory (PDI), a 13-item self-assessment scale at baseline (prior to chemotherapy), during chemotherapy (day 42), and six months and one year following completion of therapy. Although there were no differences at baseline between the two groups, increased psychological distress was observed among women randomized to the dose-dense regimen. Importantly, patients in the dose-dense treatment arm had a higher incidence of side effects, including anemia, alopecia, mucositis, diarrhea, bone pain, and fatigue, which may have contributed to their increased psychological distress. At subsequent evaluations after completion of treatment, psychological distress was again similar in the two arms.

Cognitive deficits (e.g., problems with memory and concentration) following chemotherapy have been reported, but the research to date has

been limited [33]. Mounting evidence suggests that standard adjuvant chemotherapy may result in residual cognitive dysfunction, although small sample sizes and methodologic limitations weaken the conclusions that can be drawn from the available studies [34–36]. Limited data exist on the effects of high-dose chemotherapy on cognitive function. In a randomized study comparing transplant to standard chemotherapy, Forbes and colleagues found that cognition, measured by the cognitive functioning subscale of the QLQ-C30, was lower at a six-month follow-up than baseline but returned to baseline levels by one year [26]. Van Dam et al. utilized a series of neuropsychologic tests to assess the prevalence of cognitive deficits in women with high-risk breast cancer randomly assigned to either high-dose or standard-dose adjuvant chemotherapy plus tamoxifen [36]. Patients also were queried regarding cognitive problems, health-related QOL, anxiety, and depression. Thirty-four patients were treated with high-dose chemotherapy plus tamoxifen, and 36 patient received standard-dose chemotherapy plus tamoxifen. They were compared to a control group of 34 women with stage I breast cancer not treated with chemotherapy. The average time since completion of the last nonhormonal therapy was two years. Thirty-two percent of patients treated with high-dose chemotherapy demonstrated evidence of cognitive impairment, compared with 17% of patients treated with standard-dose chemotherapy, and 9% of controls. Patients treated with high-dose chemotherapy had 8.2 times higher risk of cognitive impairment compared with controls (odds ratio; 95% confidence interval [CI] = 1.8-37.7). In comparison with the patients who received standard-dose chemotherapy, the risk of impairment after high-dose therapy was 3.5-times higher (95% CI = 1.0-12.8). Although a measurable diminution in cognitive functioning was apparent, the impact of the impairment on patients' daily lives is unknown [33].

In summary, reasonable evidence exists that treatment with high-dose chemotherapy is associated with psychological distress in some patients that may persist for years after treatment. While there is no convincing evidence that adverse psychological symptoms have a deleterious effect on recurrence or survival, QOL is undoubtedly affected [37–40]. A psychological assessment should be part of follow-up care after high-dose therapy. Interventions, such as support groups, psychotherapy, or medications may be useful in some patients [41].

SEXUAL FUNCTIONING

Breast cancer and its treatment may result in significant difficulties with sexual functioning. The source of these difficulties is likely multifactorial. Treatment often leads to menopause in younger women, resulting in the sudden onset of menopausal symptoms and impaired fertility. In addition, patients experience increased fatigue, decreased libido, and mood disturbances. The stress of having cancer and undergoing a very intensive treatment places added strain on many relationships. Winer et al. reported that among women at least one year post-transplant, 67% reported decreased sexual interest and 88% reported decreased sexual activity [21]. Furthermore, 60% reported pain or difficulty with intercourse, and 51% reported feeling physically unattractive at the time of interview. The proportion of women reporting these symptoms at least one year after transplant was significantly higher than the proportion of women who recalled having had these complaints one year prior to transplant. The authors acknowledged that recall bias may have contributed to changes in sexual functioning, and the extent to which treatment-induced menopause led to sexual difficulties is unknown. Notably, stage of disease at the time of transplant, as well as disease status at the time of the interview, did not correlate with sexual functioning. Overall QOL, as determined by the FLIC, did not seem to be influenced by sexual dysfunction.

Frank discussions about sexual issues may prove beneficial and ultimately improve survivors' QOL [19]. Asking women who have undergone high-dose chemotherapy about possible difficulties with sexual functioning may uncover areas of

significant distress. Women who are distressed about changes or problems with sexual functioning should be referred for further evaluation and treatment.

ROLE FUNCTIONING AND EMPLOYMENT STATUS

Role functioning and employment status have been increasingly recognized as important components of QOL. In a randomized trial comparing high-dose therapy to standard chemotherapy, Forbes et al. found that role functioning, as determined by the role functioning subscale items on the QLQ-C30, had declined for both treatment arms six months after treatment, but improved to higher than baseline levels by one year [26]. Hann et al. reported that by at least three months after transplant for breast cancer, only 37% of women had returned to work full-time, and an additional 16% were working part-time [12]. Winer et al. found most patients who were employed outside the home prior to transplant ultimately returned to work, with the median time away from work being 48 weeks [21]. Patients who returned to work reported significantly higher FLIC scores. However, Macquart-Moulin et al. reported that 42% of women who were previously employed were not working one year after transplant, with the remaining women evenly split between full-time and part-time work [25]. These data demonstrate the significant impact of breast cancer and high-dose therapy on a woman's ability to conduct her usual daily activities even more than a year following transplant.

DELAYED COMPLICATIONS AND LONG-TERM EFFECTS

While autologous transplants are not associated with many of the long-term adverse effects characteristic of allogeneic transplant, such as graft-versus-host disease and the infectious complications of chronic immunosuppression, the preparatory regimens used for autologous transplants may still have significant long-term or delayed side effects. These include prolonged cytopenias, secondary malignancies (particularly myelodysplasia and leukemia), pulmonary complications such as radiation or chemical pneumonitis, impaired endocrine function, and fertility problems [42,43]. Such complications, although uncommon, may significantly compromise patients' quality of life.

CONCLUSIONS

Although the existing research has been limited, self-reported overall QOL appears to be relatively favorable for most patients with breast cancer following high-dose chemotherapy with stem cell transplantation. For those who remain disease free, overall QOL is generally preserved. Nevertheless, many patients report difficulties in one or more areas of functioning. It is likely that substantial adaptation to chronic disability occurs in many patients, to some extent accounting for their favorable assessment of QOL [19]. In light of this finding, the potential for improvement with targeted interventions may be considerable. For example, among 25 patients undergoing autologous transplant (36% for breast cancer), physical exercise during hospitalization correlated significantly with improved QOL, even after controlling for demographic and medical variables [44].

Ongoing and recently reported studies comparing high-dose chemotherapy with conventional therapy have assessed QOL prospectively, with serial measurements extending from baseline to several years following treatment [28]. Such studies better characterize QOL and the specific effects of high-dose therapy. Future studies of high-dose chemotherapy for breast cancer, and other malignancies, should consider the inclusion of formal assessment of multidimensional QOL. Such studies should focus on interventions as well as better characterizing and documenting the impact of impairment on patients' day to day lives.

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Informing Clinical Trial Participants About Study Results

[Commentary]

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Outline

OF THE 1.3 MILLION INDIVIDUALS DIAGNOSED WITH cancer each year in the United States, [1] a substantial minority participate in clinical trials. [2,3] When patients agree to enter these trials, they expect their physicians to provide full and detailed information about the study. In addition, the success of the research may be influenced by how well patients are informed. [4] Following completion of a clinical trial, participants are not routinely informed about the aggregate study results unless this information would influence their future care. However, anecdotal experience suggests that many patients who participate in clinical trials are interested in the experience of other patients enrolled in the study and in learning about the aggregate results. A recent consensus conference recommended that the results of clinical trials should be made available to participants and suggested that providing participants with results, both positive and negative, should be considered the "ethical norm." [5] Currently, there is clear disparity between this recommendation and what actually occurs. This article examines the implications of offering trial results to study participants and the steps necessary before results could be routinely provided. Clinical trials of cancer therapies are used as an example, although the issues may extend to many types of clinical research.

As part of informed consent, clinical researchers agree to alert participants about any new information that may affect their willingness to remain in the study. When the results of a clinical trial would make a difference in a patient's current or future care, researchers are obligated to inform study participants of the findings. [6] For example, when the results from the National Surgical Adjuvant Breast and Bowel Project P-1 study [7] indicated that 5 years of tamoxifen therapy significantly reduced the risk of breast cancer compared with placebo, women

in the placebo group were contacted and offered the opportunity to take tamoxifen. More often, however, the results of a study will not change the immediate care of the study participant. The results of a randomized adjuvant chemotherapy trial will not alter the care of a study participant who is 5 years out from trial participation and is disease free. In settings such as this, the results of clinical trials are often presented at research conferences and published in peer-reviewed journals, but there is generally no provision to provide feedback directly to the study participants. In contrast, for clinical trials that are terminated early, such as those demonstrating harm, participants should be notified before the results are widely disseminated. The following discussion refers to those situations in which results would not affect a study participant's medical care or willingness to remain in the study.

The concept of providing results to participants is not a new idea. In response to problems that have resulted from research in aboriginal communities, all research reports are shared with community members at the time of study completion. [8,9] Such "participatory research" attempts to break down the distinction between researcher and research participants and to build collaboration between the parties. The aim of participatory research is "... to empower research subjects to assume ownership of the research process and to use the results to improve their quality of life." [10,11] For research in aboriginal communities, the partnership between researchers and study participants extends to dissemination of the results. Community members remain full partners throughout the research and are often included as authors of publications in scientific journals. [10] Researchers at the Nurses' Health Study, a prospective cohort study of more than 120 000 women, routinely send an annual mailing to all study participants summarizing the aggregate findings from the studies that have used data from the study. The researchers do this both as a courtesy and as part of their effort to retain participants (G. Colditz, oral communication, August 14, 2000). While these examples represent large observational studies, these models could be applied with modification to the clinical trial process.

To our knowledge, no routine mechanism is in place to share study results in large cooperative groups in adult oncology. Although the results of occasional studies may be shared with study participants, we are not aware of any systematic approach to this issue, nor do we know of any effort to assess outcomes of sharing results. Within the pediatric oncology community, a bioethics committee is currently developing mechanisms to share study results with pediatric patients and their families. [12]

Potential Benefits of Providing Trial Results

To date, there is no published evidence to suggest either positive or negative outcomes of sharing clinical trial results. One might wonder why clinical researchers have not routinely offered study participants the results of clinical trials. In general, the aim of clinical research should be to treat each individual participant with the utmost respect, as an end in and of himself or herself, and as a partner in research. In support of this approach, results should be shared, as doing so could be considered the correct course of action when working toward a common goal with a partner. At a minimum, trial results should be offered as a reward, acknowledgment, or sign of appreciation for involvement in research, as altruistic motives often influence an individual's decision to participate in a clinical trial. [13,14]

From a utilitarian perspective, providing clinical trials results to study participants might "maximize the good," although no empiric data support this premise. Sharing results with individuals and the lay public in general could result in better patient-physician communication, which would likely lead to greater satisfaction with care. [15] From a research standpoint, sharing results might lead to patients having a better understanding of clinical trials, thereby bolstering clinical trials accrual and ultimately leading to improvements in patient care.

Certain difficult situations would be averted by routinely offering clinical trial results to participants. When recent clinical trials suggested that high-dose chemotherapy with bone marrow/stem cell transplant was no better than standard dose chemotherapy for breast cancer, [16–18] one of the many issues that arose was the perceived late delivery of this information to the community of breast cancer patients. Some patients and family members expressed anger and distress that they learned of the findings predominantly from the media and not from their physicians. [19] Implicit in their distress was a sense that the trust between physician-researchers and the study participants had been broken. A similar situation occurred in the case of a study of complementary therapy for women with breast cancer. [20] The study demonstrated that women who had been to a cancer help center were 3 times more likely to relapse and 2 times more likely to die than women who had not been to the center. [21] The results were initially reported on the evening news; thinking the study was still ongoing, participants knew nothing of the results until this public disclosure. [20] It is not surprising that patients in both circumstances felt personal disappointment, as well as a sense of abandonment and betrayal.

Barriers to Providing Trial Results

There are several potential barriers to providing the results of clinical trials to study participants. Perhaps the most significant argument against providing results is that many patients might not want the results. Reactions to results may be heavily influenced by an individual's coping style, how well he or she dealt or is dealing with the illness, the extent to which he or she was involved in the decision-making process surrounding treatment, and a range of factors related to the patient's current mental and physical health. [22–25] Furthermore, an individual's response to receiving trial results could be affected by how the patient fared with the treatment from the standpoint of both efficacy and toxicity and the actual results of the trial. Several possible scenarios might engender significant patient distress. For instance, in a study in which the investigational drug was effective in only 15% of participants, a patient who did not benefit from a study therapy may find learning the results more distressing than a patient who was among the 15% who responded to the new treatment. The situation could potentially become even more complicated in the context of a randomized trial.

Some patients who had been previously treated as part of a clinical trial might not want to be reminded of the treatment or the disease. It is conceivable that contacting patients with results of their trials, which sometimes are not available until years after the patient has received active treatment, would cause emotional distress. In an effort to address this concern, patients could be asked at the time of study enrollment if they wish to be offered trial results in the future.

The situation becomes more complex when the study participant has died or is not capable of receiving the results himself or herself. If researchers approach next-of-kin with the results of a clinical trial, it is not difficult to imagine that such interactions might have significant psychosocial repercussions. Researchers would need to anticipate negative reactions and be prepared to provide the necessary support.

Several issues involving health care professionals also must be considered. First, an obligation to offer results to patients would necessitate the use of substantial resources. Individual study participants may want more or less information, and it could become quite time-consuming for the clinical researchers to handle such needs. Second, some clinicians may be reluctant to discuss trial results with patients in an effort to protect them from "bad news," especially if they deem sharing study results unnecessary. Such paternalism may mask self-protection on the part of the clinician and may ultimately have negative consequences if patients learn of trial results from other sources. Although paternalism has been the dominant approach historically, this model has been challenged in recent years by patients, physicians, researchers, and medical ethicists who favor a more collaborative relation between physicians and patients. [26]

Another possible barrier to sharing trial results involves how researchers view the clinical trials process. Although physician-researchers generally consider an individual's care first when enrolling a patient in a study, the primary goal of clinical research is to seek generalizable knowledge. 6 Such knowledge, or even the actual treatment received, will not necessarily benefit an individual in the trial. The reality that the physician's own patient, with whom the clinician has a therapeutic relationship, may not derive benefit could be difficult for the physician to face, underscoring an important conflict. Because some clinicians may have difficulty integrating their role as both clinician and researcher, they may be subject to a form of "therapeutic misconception." 27,28 This misconception can exist if clinical researchers come to believe that the research procedures or therapy they recommend to a patient are designed primarily for the benefit of that patient, rather than for improvement of the care of future patients. 27,28 A duty to offer patients the results of clinical trials, particularly when the results are not favorable, would force physician-researchers to confront this inherent conflict. Open dissemination of trial results may be one way to emphasize the research nature of clinical trials to both clinicians and patients, who might otherwise conflate trial participation with standard clinical care. Counteracting this misperception may represent another benefit of sharing trial results.

How to Provide Clinical Trial Results

If researchers were to routinely offer trial results to participants, several important issues arise. First, the fact that results of a study will be offered and provided in the future should be built into the informed consent process so that patients are aware of the plan and have the opportunity to decline future contact with the investigators. Second, the timing of sharing results could be quite complicated. Guidelines are needed for determining the appropriate time at which results would be offered to participants. Plans for dissemination of results could then be built into individual study protocols, with careful consideration of when to share findings from interim analyses and information on adverse effects, when appropriate. Optimally, study results should be offered and provided to participants prior to public disclosure. Third, support for investigators from funding agencies will need to be provided if study results are to be shared responsibly. Fourth, future research will need to address the best means to communicate study results to trial participants. This and many other unanswered questions should be studied systematically with careful attention to patient preferences and outcomes of sharing results.

Conclusion

There are a variety of important and unanswered questions regarding both patient and clinician attitudes toward sharing clinical trial results, the potential impact of routinely sharing results, and methods by which results can be shared in a responsible manner. On the surface, the concept of providing clinical trial results might seem straightforward, but putting such a plan into action will be much more complicated. Communication with patients following participation in a clinical trial represents an important and often overlooked aspect of the patient-physician relationship. The sharing of trial results has implications for efforts to improve medical care. Careful exploration of this issue, both from the patient and clinician-researcher perspective, is warranted. Although public opinion regarding participation in clinical trials is positive, clinical trial accrual remains low. 2,29 The failure to provide information about study results may be one of the many factors that adversely affect accrual. Better understanding of physician-researcher and patient attitudes and preferences, and development of effective mechanisms to share trial results with study participants, should help to enhance patient-physician communication and improve the clinical research process.

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Side Effects of Chemotherapy and Combined Chemohormonal Therapy in Women With Early-Stage Breast Cancer

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The decision to receive chemotherapy or chemohormonal therapy involves careful consideration of both the potential benefits and possible risks of therapy. There are substantial short- and long-term side effects from chemotherapy. By convention, short-term side effects include those toxic effects encountered during chemotherapy, while long-term side effects include later complications of treatment arising after the conclusion of adjuvant chemotherapy. These side effects vary, depending on the specific agents used in the adjuvant regimen as well as on the dose used and the duration of treatment. There is also considerable variability in side effect profile across individuals. This review will focus on the short- and long-term toxicity seen with the most commonly used adjuvant chemotherapy and chemohormonal therapy regimens. [J Natl Cancer Inst Monogr 2001;30:135–42]

The role of adjuvant systemic therapy has been studied extensively in women with early-stage breast cancer. Chemotherapy and chemohormonal therapy improve disease-free and overall survival in women with operable breast cancer *(1)*. The absolute benefits of adjuvant chemotherapy vary depending on the treatment regimen, the characteristics of the tumor (e.g., hormone receptor status), the medical and demographic characteristics of the woman (e.g., comorbid conditions and age), and the absolute risk of disease recurrence. In women with a relatively high risk of disease recurrence, the improvement in disease-free and overall survival associated with adjuvant chemotherapy can be quite substantial. In contrast, in women with small tumors and/or negative lymph nodes, the absolute benefits of treatment may be quite small. Decision making about adjuvant therapy—particularly adjuvant chemotherapy—can be complex. Women and their physicians must consider the potential benefits of treatment as well as the possible risks and anticipated side effects.

Side effects from chemotherapy can be divided into short-term effects and long-term effects. Table 1 lists short-term and long-term effects of adjuvant chemotherapy. Short-term effects typically occur during the course of treatment and generally resolve within months of the completion of therapy. In contrast, long-term effects can have a later onset and sustained impact—often lasting for many years. In the case of some of the rare long-term effects, many years may elapse before any symptoms develop.

Short-Term Side Effects

The most frequently encountered short-term side effects seen with standard adjuvant chemotherapy regimens and their relative frequency and severity are listed in Table 2. Fatigue, which is listed as a short-term effect, has been recognized in recent years as a common side effect of cancer chemotherapy *(2–7)*. The assessment of fatigue with standard toxicity grading scales has probably underestimated the prevalence of this problem, and there are few studies of women receiving adjuvant chemotherapy that have detailed self-reports of fatigue. For this reason, it is particularly difficult to determine the prevalence, severity, and duration of fatigue in women receiving adjuvant chemotherapy. There is evidence that some patients cite difficulties with fatigue for months and even years after adjuvant chemotherapy *(7,8)*, but it is not known to what extent such findings differ from age-matched control subjects. Because of the presumed underreporting of fatigue in many studies, it is not possible to assess with confidence the prevalence and severity of fatigue associated with different adjuvant regimens.

Treatment-related side effects are often gauged by standardized criteria from the National Cancer Institute. In Table 2, we have characterized the frequency and usual severity of the most common short-term side effects using the reported toxic effects in 12 adjuvant trials conducted in the late 1980s and 1990s *(9–21)*. We have focused on recent trials that have used many of the modern supportive care measures that are currently available; however, some of these trials were conducted before the availability of the serotonin antagonists for the prevention and treatment of emesis. Therefore, reported rates of nausea and vomiting may be somewhat higher than would be seen today. Side effects characterized as mild correspond to reported grade 1 or 2 toxic effects, whereas those characterized as moderate and severe correspond to grade 2 or 3 and grade 3 or 4 toxic effects, respectively. We characterized the frequency of side effects as follows: fewer than 1%, almost never; 1%–5%, rare; 6%–20%, uncommon; 21%–50%, common; 50%–95%, frequent; and greater than 95%, almost always. Similar regimens administered in different trials and by different investigators *(9–21)* had remarkably similar side effect profiles. It should be noted that, although neuropathy is listed as a short-term side effect, the extent to which this persists over time has not been well characterized.

In general, the non-anthracycline-containing regimens are associated with fewer grade 3–4 short-term toxic effects than are anthracycline-based regimens. Neuropathy is rarely seen with either the combination chemotherapy of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or the methotrexate and 5-fluorouracil (MF) regimens. In contrast, emesis (i.e., nausea and/or vomiting), alopecia, and myelosuppression (principally neutropenia) are seen commonly to very commonly with the CMF regimen. Mucositis is seen less frequently with intrave-

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See "Note" following "References."

Appendix 3

Table 1. Side effects of chemotherapy

Short-term effects	Long-term effects
Emesis	Premature menopause/infertility
Nausea	Weight gain
Stomatitis	Cardiac dysfunction
Alopecia	Leukemia/MDS*
Myelosuppression	Congnitive dysfunction†
Thromboembolism	
Myalgias	
Neuropathy‡	
Fatigue‡	

*MDS = myelodyspastic syndrome.
†Possible long-term effect; studies are preliminary in nature.
‡May be both short-term and long-term effect.

nous CMF, compared with oral CMF. Despite the frequency of these side effects, they are often of either mild or moderate severity. Complete alopecia can be seen with these regimens, but when alopecia occurs with CMF, it is frequently partial. Because cyclophosphamide is administered orally for a total of 84 days in the classic oral CMF regimen, nausea with this regimen is sometimes more persistent than with other programs. The MF with leucovorin regimen, used in National Surgical Adjuvant Breast and Bowel Project (NSABP) protocols B-14, B-19, and B-20 *(11,13,22)*, is generally associated with even fewer grade 3–4 short-term toxic effects than classic cyclophosphamide-containing regimens. Because of concern that the MF with leucovorin regimen is inferior to CMF *(11)*, it is not used frequently, although when it is used in combination with tamoxifen, the benefits of CMF and MF appear to be similar *(13)*.

Short-term side effects with the anthracycline-based regimens *(15,17,19,20)* tend to be more frequent and more severe than those with non-anthracycline-containing treatment. Emesis and myelosuppression are very common with all of these regimens and can be severe in nature. Complete alopecia is seen with almost all anthracycline-based regimens. Mucositis appears to be more common with the 5-fluorouracil-containing regimens, such as combination chemotherapy with cyclophosphamide, doxorubicin (Adriamycin), and 5-fluorouracil (CAF) or 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC), as opposed to doxorubicin and cyclophosphamide (AC). When paclitaxel is used as part of a sequential regimen, neuropathy and myalgias can be seen occasionally, although symptoms are generally mild. Of note, when higher doses of paclitaxel (i.e., 225 mg/m^2) were used, as in NSABP B-28, the neuromuscular toxicity was more frequent and may have been more severe *(23)* than with lower doses (i.e., 175 mg/m^2), as those used in Cancer and Leukemia Group B (CALGB) 9344.

An increased risk of thrombosis has been reported in several trials of adjuvant therapy. The risk of thrombosis appears to occur during active treatment and to abate over time. In a trial comparing shorter and longer chemotherapy regimens, Levine et al. *(24)* reported an increased risk of thrombosis on both arms, but only during the period of active treatment. Women on the shorter-duration chemotherapy arm stopped having thrombotic episodes when chemotherapy was stopped, whereas women in the longer arm continued to have thrombotic events for the full duration of their treatment. There is evidence that the use of concurrent chemohormonal therapy results in a higher rate of thromboembolic complications than does the use of tamoxifen alone *(13,25–27)*. In NSABP B-20 *(13)*, in which women were randomly assigned to receive tamoxifen alone or administered concurrently with either MF or CMF, the incidence of thrombosis was 1.9% in the tamoxifen-treated group, compared with 6.5% and 7.5% in the patients treated with tamoxifen plus MF and tamoxifen plus CMF, respectively. In a Canadian trial comparing tamoxifen alone with chemotherapy plus tamoxifen, the incidence of thrombosis was 2.6% on the tamoxifen-alone arm and 13.6% in the CMF plus tamoxifen arm ($P<.0001$) *(27)*. The use of concurrent chemohormonal therapy may also be associated with a higher rate of thrombosis than chemotherapy alone *(26)*. Given the greater risk of thrombosis associated with

Table 2. Frequency and usual severity of short-term side effects associated with adjuvant breast cancer chemotherapy regimens*

	Nausea	Vomiting	Diarrhea	Stomatitis	Alopecia	Neutropenia	Febrile neutropenia or infection	Thrombocytopenia	Neuropathy	Myalgias
Toxicity regimen										
CMF (oral cyclophosphamide)	Frequent, +/++	Common, +	Common, +	Common, +	Frequent, partial–total	Frequent, ++/+++	Rare	Frequent, +	Almost never†	Almost never†
CMF (all intravenous)	Common, +/++	Frequent, +	Common, +	Uncommon, +	Frequent, partial–total	Frequent, ++/+++	Rare	Uncommon, +	Almost never†	Almost never†
MF	Common, +	Common, +	Common, +/++	Uncommon, +	Uncommon, minimal	Rare, +	Almost never	Almost never†	Almost never†	Almost never†
AC	Frequent, +/++	Common, +/++	Uncommon, +	Common, +/++	Almost always, total	Frequent, ++/+++	Rare	Uncommon, +	Almost never†	Almost never†
AC-tamoxifen (tamoxifen only)	Rare, +	Rare, +	Rare, +	Rare, +	Almost always, total	Common, +	Rare	Almost never†	Uncommon, +/++	Common, +/++
CEF/FAC (oral cyclophosphamide)	Frequent ++/+++	Frequent, +/++	Common, +/++	Frequent, ++/+++	Almost always, total	Almost always, +++	Common	Frequent, +/++	Uncommon, +	Uncommon, +
CAF/FAC/FEC 100 (all intravenous)	Common, ++/+++	Common, +/++	Common, +/++	Frequent, +/++	Almost always, total	Frequent, +++	Common	Frequent, +/++	Uncommon, +	Uncommon, +

*Frequency: almost never = less than 1%; rare = 1%–5%; uncommon = 6%–20%; common = 21%–50%; frequent = 51%–95%; almost always = more than 95%. Severity (for all toxic effects excluding alopecia): + = mild; ++ = moderate; +++ = severe. CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; AC = doxorubicin and cyclophosphamide; CAF = cyclophosphamide, doxorubicin, and 5-fluorouracil; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; MF = methotrexate and 5-fluorouracil; CEF = cyclophosphamide, epirubicin, and 5-fluorouracil; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide.
†Not recorded in trials *(9–21)*.

tamoxifen in women over 50 years *(28,29)*, combination therapy may be particularly problematic in older women *(27)*. A U.S. Intergroup Trial *(30)* compared CAF followed by tamoxifen with CAF and concurrent tamoxifen in postmenopausal women. To date, no results comparing these two arms of the study have been reported concerning either efficacy or thrombosis risk. Because of concern about the increased risk of thrombosis, many physicians choose not to administer chemotherapy and tamoxifen concurrently outside of a clinical trial.

Because short-term side effects typically resolve with therapy, the duration of treatment has a major impact on the total side effect burden that a woman may experience. Most treatment regimens are approximately 4–6 months in duration. The AC regimen, however, is substantially shorter and is completed in 12 weeks. The last dose of AC is actually administered 9 weeks after the first dose *(9)*, and, as a result, the duration of short-term side effects is reduced. In a randomized trial comparing AC with 6 months of CMF, investigators from the NSABP concluded that the shorter regimen was associated with a lower total side effect burden *(9)*. The perception that AC is a relatively well tolerated regimen has led to its widespread use over the past decade.

The impact of adjuvant chemotherapy on quality of life has been evaluated in several studies. The International Breast Cancer Study Group randomly assigned patients to either three or six cycles of chemotherapy and demonstrated a more rapid improvement in quality of life with the shorter treatment regimen compared with the longer treatment regimen *(31)*. Other investigators have demonstrated that quality of life improves rapidly with the completion of therapy. Levine et al. *(15)* showed that quality of life actually improved throughout the course of adjuvant therapy, suggesting some measure of psychological and physical adaptation to a new diagnosis of breast cancer, surgery, and ongoing chemotherapy. Since no studies have measured quality of life before the diagnosis of breast cancer, it is unknown when or if quality of life following adjuvant therapy returns to the prediagnosis baseline. Research in breast cancer survivors suggests that the majority of women diagnosed with early-stage breast cancer return to fully active lives by 1 year after diagnosis, although women who received adjuvant chemotherapy may be more likely to have some residual symptoms, such as sexual dysfunction *(32,33)*. More research is clearly needed to characterize the recovery trajectory, in terms of both physical and psychological health, following a course of adjuvant chemotherapy.

Despite the high prevalence of breast cancer among older women, researchers have only recently focused on treatment questions in this patient group. Few randomized trials have included many women over 65 years of age *(34–36)*. It is widely assumed that older patients are less tolerant of chemotherapy than younger patients. Although a few small studies have reported significantly increased toxicity in the elderly, recent larger studies provide evidence to the contrary. Crivellari et al. *(37)* studied the use of adjuvant CMF and tamoxifen in elderly women. Although women aged 65 years or older had greater hematologic and mucosal toxicity than younger women, quality-of-life measures suggested that the subjective burden of treatment was similar for older and younger patients. Begg and Carbone *(38)* examined 19 Eastern Cooperative Oncology Group studies that included a total of 780 patients aged 70 years or older. In comparison with younger individuals in the trials, older patients had increased hematologic toxicity; otherwise, the incidence of severe toxic effects was similar between groups. In a more recent prospective study, Dees et al. *(39)* treated 44 women aged 35–79 years with early-stage breast cancer with four cycles of adjuvant AC chemotherapy. In this cohort, although myelosuppression was increased in older women, neutropenic complications, alteration in cardiac function, and change in quality-of-life scores were not significantly related to age. Pharmacokinetic analyses did not demonstrate age-related differences in the clearance of doxorubicin or cyclophosphamide. Although patients in these studies may represent a highly selected group, it is reassuring that the older patients appear to tolerate chemotherapy nearly as well as the younger patients. Additional research in this area is clearly warranted.

Long-Term or Sustained Side Effects

In addition to the short-term side effects from chemotherapy, there are a number of sustained or long-term consequences of treatment. Some of these long-term effects, such as premature ovarian failure, are commonly seen in certain subgroups of patients. Others, such as secondary leukemia, are extremely rare consequences of treatment. Nevertheless, these rare effects must be considered in decision making about adjuvant therapy, particularly when the absolute benefits associated with treatment are of small magnitude.

Premature Ovarian Failure

Premature ovarian failure or premature menopause is a common consequence of adjuvant chemotherapy in premenopausal women. The risk of premature menopause appears to be related to patient age, the specific chemotherapeutic agents used, and the total dose administered. The effect of treatment duration and dose intensity, independent of total dose, is uncertain. While premature ovarian failure may have a beneficial effect on breast cancer prognosis *(40)*, particularly in women with hormone receptor-positive tumors, early menopause may have important physiologic and psychosocial consequences. For women who wish to consider becoming pregnant after breast cancer, risk of infertility following chemotherapy is a major concern. Other problems related to premature ovarian failure include menopausal symptoms, such as hot flashes, genitourinary problems, and both psychological and psychosexual difficulties *(33,41,42)*. Women who experience premature menopause have accelerated bone mineral density loss *(43–46)*. Premature menopause may also contribute to increased cardiovascular morbidity, although data to support this concern in women with breast cancer are lacking. For many of these symptoms or complications, there are nonhormonal interventions available *(47)*. However, patients commonly express concerns over menopausal symptoms and their bone and heart disease risk during longer follow-up.

Table 3 shows the proportion of women who experience premature menopause with adjuvant chemotherapy *(48)*. The table is broken down by treatment regimen and age. The vast majority of women over the age of 40 years experience menopause after treatment with CMF or cyclophosphamide, epirubicin, and 5-fluorouracil (CEF). In women under the age of 40 years, the risk of ovarian failure from these regimens is lower but is by no means uncommon. MF has been reported to be associated with an approximately 10% incidence of premature menopause, but this has not been analyzed as a function of patient age. AC is associated with a lower incidence of premature menopause in

Table 3. Risk of premature menopause by regimen and age*

Regimen	Duration, mo	Incidence of amenorrhea, %	
		<40 y	≥40 y
CMF-based	6	31–38	81–96
	12	51–77	83–98
FEC	6	23	89
AC	3	13	57–63
MF	6	~10	

*Adapted with permission from Burstein and Winer in J. R. Harris' Diseases of the Breast, 2000 *(48)*.

CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; AC = doxorubicin and cyclophosphamide; MF = methotrexate and 5-fluorouracil.

both younger and older women, probably because of the lower cumulative dose of cyclophosphamide with this regimen. The effect of adjuvant taxane therapy on premature ovarian failure is not well characterized. In one small retrospective study *(49)*, the addition of paclitaxel to AC did not appear to substantially increase the overall risk of chemotherapy-related amenorrhea; however, larger studies are needed to make any definitive conclusions. In women under the age of 30 years, premature ovarian failure with any of the available regimens is distinctly uncommon. Three separate reports *(50–52)* have provided estimates for the incidence of premature ovarian failure in 20% or fewer women. In two of these studies *(50,52)*, there were no patients under the age of 30 years who experienced premature menopause. In another report, Goodwin et al. *(53)* evaluated the incidence of ovarian failure in women who received no systemic therapy compared with those who received either chemotherapy or chemotherapy followed by tamoxifen. Young women (under the age of 30 years) had a very low incidence of menopause regardless of the therapy received. As expected, the incidence of chemotherapy-related amenorrhea increased with age.

Chemotherapy-related amenorrhea may be reversible in that some women will resume menstrual function months or years after treatment. However, the vast majority of women who remain amenorrheic 1 year after treatment will not regain ovarian function. The possibility of delayed (i.e., occurring even years after treatment) premature menopause has not been explored thoroughly. In the pediatric oncology population, there is evidence that adolescent girls who receive chemotherapy experience an earlier than expected menopause as they age *(54)*. It is certainly plausible that a young woman who receives chemotherapy and does not experience chemotherapy-related amenorrhea will nevertheless go through menopause earlier than she would have in the absence of chemotherapy.

Weight Gain

Weight gain has been reported in 50% or more of women receiving adjuvant chemotherapy, with mean gains of 2.5–5.0 kg *(55–58)*. More significant weight gain, as much as 10–20 kg, has been reported by some investigators in as many as 20% of patients. Weight gain appears to be more common in premenopausal women than postmenopausal women, and women who experience menopause with chemotherapy also seem to be at greater risk of weight gain *(55–57)*. Regimens that are longer in duration may increase the risk of weight gain, and weight gain may be less common with the shorter AC regimen *(59)*. Weight gain, particularly when substantial, can have a profound influence on a woman's physical health and psychological adaptation. In addition, retrospective studies *(60–63)* have suggested that weight gain may increase a woman's risk of disease recurrence.

The underlying cause of weight gain with chemotherapy is uncertain. For years it was assumed that weight gain occurred because women receiving chemotherapy simply ate too much. Studies that have monitored dietary intake have failed to support this view *(57,64,65)*. Preliminary evidence suggests that weight gain may be caused by decreased physical activity during therapy *(59,64,65)*. Studies *(58,59,64–66)* have also suggested that there may be changes in resting metabolic rate and that lean body mass can decline following a course of chemotherapy. Interventions focusing on exercise and on increasing lean body mass may help to ameliorate weight gain among women receiving adjuvant breast cancer chemotherapy *(65)*.

Long-Term Cardiac Effects

Cardiotoxicity has been a major concern, since anthracycline-based regimens have been used more commonly in the adjuvant setting. The incidence of anthracycline-induced cardiac dysfunction increases with the increasing cumulative amount of anthracycline (either doxorubicin or epirubicin) administered. Other risk factors may include advancing age and a history of cardiac disease *(67,68)*. In general, most adjuvant chemotherapy regimens restrict cumulative doses of doxorubicin to less than 360 mg/m^2 and of epirubicin to less than 720 mg/m^2—doses thought to fall within a relatively safe range with clinically acceptable rates of cardiac complication. Valagussa et al. *(69)* reported a 0.8% incidence of congestive heart failure in a group of more than 500 women who received approximately 250 mg/m^2 of doxorubicin, with a median follow-up of 80 months. Zambetti et al. *(70)* performed a more detailed assessment of cardiac function in a group of 355 women who were disease free at a median follow-up of 11.5 years. Forty-four percent of the women received CMF only, and the remainder received CMF followed by doxorubicin, with a median cumulative doxorubicin dose of approximately 300 mg/m^2. Women were assessed by physical examination, history, electrocardiogram, and echocardiogram. Although clinical congestive heart failure was very rare in both groups, 8% of the patients receiving doxorubicin were characterized as having systolic dysfunction, defined as an ejection fraction of less than 55%. In contrast, fewer than 2% of the CMF group had evidence of systolic dysfunction. In a recent U.S. Intergroup trial using CAF in postmenopausal women, the reported incidence of congestive heart failure was approximately 2% *(30)*. Of note, the patient population was somewhat older than in many adjuvant trials, and the total planned dose of doxorubicin was 360 mg/m^2.

The existing data concerning long-term cardiotoxicity are relatively reassuring, and the absence of clinical symptoms in the vast majority of patients is encouraging. However, the possibility of long-term subclinical systolic dysfunction, as seen in the Zambretti study, merits further investigation. Physicians can counsel women without pre-existing cardiac disease that the incidence of symptomatic cardiac problems with anthracycline-based regimens is extremely rare. There is reason to have some limited concern about the potential for very long term toxicity; it is not presently known whether anthracycline exposure increases the risk of cardiac compromise with subsequent cardiac stressors (e.g., hypertension) or a subsequent cardiac event (e.g.,

a myocardial infarction). In women with baseline cardiac dysfunction or in those who are at risk for compromise based on their medical history, it may be prudent to evaluate cardiac function before and after anthracycline-based adjuvant therapy, although data in support of this are limited.

Concern has been raised that breast/chest irradiation would increase the risk of cardiac toxicity. In a randomized trial of 5 versus 10 cycles of AC, there was an increased risk of cardiac events in the group of women who received 10 courses of treatment (median cumulative dose of doxorubicin, 442 mg/m^2) *(71)*. This effect seemed to be more pronounced in women who received high dose volume of cardiac irradiation. There appeared to be no excess cardiac risk in women who received five cycles of AC (median cumulative dose of doxorubicin, 225 mg/m^2) with radiation therapy. In a retrospective analysis from Valagussa et al. *(69)*, a total of four (0.8%) of 501 women treated with doxorubicin developed congestive heart failure, with a median follow-up in excess of 6 years; of the 114 women who received doxorubicin and left-sided breast irradiation, three (2.6%) developed congestive heart failure. Any increased concern with left-sided irradiation and the use of doxorubicin is probably less worrisome with the availability of modern radiation planning.

Chemotherapy-Associated Leukemia

Leukemia or myelodyspastic syndromes (MDSs) associated with adjuvant therapy are very rare, but devastating, complications of treatment. Curtis et al. *(72)* conducted a case–control study in almost 82 700 women who were treated for breast cancer during the 1970s and 1980s. On the basis of their work, the total dose of cyclophosphamide appears to be an important risk factor, with a substantially higher risk in women who receive more than 20 000 mg of the drug. With typical CMF regimens, which use significantly lower cumulative doses of cyclophosphamide, Curtis et al. *(72)* estimated that an additional five cases of leukemia would be seen in 10 000 women over the course of 10 years. Other investigators have used very different methodologies, making it difficult to compare across studies and with different regimens. There is some suggestion that the risk with anthracycline-based regimens may be greater than with classic CMF type regimens *(12,15,73–78)*. With anthracycline-based regimens, the overall incidence of leukemia in women with breast cancer after standard-dose adjuvant therapy is approximately 0.1%–1.5% at 5–10 years' follow-up *(12,15,30,77,79)*. In studies with 6 months of adjuvant anthracycline and cyclophosphamide therapy (e.g., CAF), the incidence of leukemia or MDS has been found to be as high as 1.5% *(15,77)*, with an even greater risk associated with the addition of adjuvant radiation therapy *(77)*. After four cycles of standard AC chemotherapy (cyclophosphamide at 600 mg/m^2 and doxorubicin at 60 mg/m^2 per cycle), the risk is probably quite low. This regimen was used as the standard arm of NSABP protocol B-22 *(12)*, and the incidence of leukemia or MDS in this group was 0.1%, with a median follow-up of 5 years. Among women who received an increased dose or dose-intensive regimens of cyclophosphamide and doxorubicin on NSABP protocols B-22 and B-25 *(12,77)*, the incidence of leukemia and MDS was higher. In both studies, there was no benefit in disease-free or overall survival observed among women who received the higher dose or dose-intensive regimens, and rates of leukemia and MDS ranged from 0.1% to 1.2%. It is reasonable to speculate that the higher doses of cyclophosphamide, up to 2400 mg/m^2 per cycle, may have contributed to the higher frequency of leukemia and MDS in these studies. In the preliminary report of the NSABP B-28 trial *(23)*, five (approximately 0.3%) cases of leukemia developed in the approximately 1500 patients who received standard-dose AC followed by paclitaxel. Whether there is any additional increase in risk with the addition of the taxanes is unknown.

The latency period and cytogenetic abnormalities appear to be different with doxorubicin-induced leukemia than those that arise after exposure to cyclophosphamide alone *(75)*. Leukemias that are associated with exposure to alkylating agents typically present 5–7 years after treatment and are frequently preceded by an MDS. Topoisomerase inhibitors, such as anthracyclines, can give rise to secondary leukemias 6 months to 5 years after therapy. There are no methods of screening for these disorders in survivors of breast cancer, although they should be considered in the evaluation of patients in whom cytopenia develops after the treatment of breast cancer. Because of the rarity of leukemia after adjuvant therapy, concern about this complication seems most reasonable in women who are at low risk of breast cancer recurrence and who are likely to derive a very small benefit from adjuvant chemotherapy.

Cognitive Dysfunction

Cognitive dysfunction after adjuvant therapy has received increasing attention in both the medical and lay literature in recent years. Three studies have been published *(80–82)* in which women who had received or were receiving chemotherapy underwent neuropsychiatric testing and were compared with a control group. Schagen et al. *(81)* evaluated 39 women who were approximately 2 years out from six cycles of CMF (with or without subsequent tamoxifen) and compared them with 34 women who had received local therapy only. Twenty-eight percent of the CMF group, compared with 12% of the control subjects, had evidence of cognitive dysfunction, predominantly characterized by difficulties with concentration, memory, word-finding, and motor-testing. Furthermore, hormonal therapy did not appear to influence patients' self-reports of symptoms or cognitive function. In a study by van Dam et al. *(80,83)*, a dose–effect relationship was seen between chemotherapy and cognitive dysfunction. At a mean of 2 years since the completion of last nonhormonal therapy, impaired cognitive dysfunction was seen in 32% of the patients treated with high-dose chemotherapy, in 17% of the patients treated with standard-dose chemotherapy, and in 9% of the women with stage I breast cancer who did not receive chemotherapy. Brezden et al. *(82)* surveyed a group of 31 women receiving chemotherapy, another group of 40 women who had received chemotherapy in the past, and a group of healthy control subjects. Impaired cognition was seen more frequently in women on active treatment compared with control subjects, and cognitive difficulties did not appear to be related to anxiety or depression. While these results are provocative, it is important to note that, in two of the studies *(80,81)*, there was no association between self-reports of cognitive dysfunction and scores on the formal testing; the women who complained of cognitive difficulties were not the same women who performed poorly on the testing. Furthermore, in none of these studies were patients assessed longitudinally to assess for change in functioning with therapy. Anecdotally, many patients complain of what has commonly been termed "chemo brain," with complaints of forgetfulness and difficulty concentrating.

The possibility of persistent impaired cognition is of great concern to patients as they make decisions about adjuvant treatment, but neither the anecdotes nor the research studies conducted to date permit any firm conclusions. Prospective longitudinal studies are warranted to pursue the hypothesis that cognition may be impaired in women following adjuvant chemotherapy.

Summary and Conclusions

How should women and their physicians use information about side effects to make decisions about adjuvant therapy? A woman with a new diagnosis of breast cancer needs to consider her risk of disease recurrence and death in the absence of therapy, the potential benefit of chemotherapy, and her post-treatment risk of recurrence and death. For an individual woman, it is the absolute, not the relative benefit, of therapy that is important. This benefit needs to be considered in the context of the short-term and long-term side effects from treatment.

In making these decisions, women and their physicians need to know the frequency, duration, and severity of side effects. This information, at least for broad groups of women, is available. Unfortunately, for many of the side effects, clinicians have relatively little ability to predict who is at greater or lesser risk of experiencing a given adverse effect. Improving the ability to predict an individual woman's risk of both long- and short-term side effects with various treatments will allow her to make an even more informed decision regarding therapy. Perhaps even more importantly, the impact of side effects on a woman's ability to carry on her daily activities has not been well evaluated. Many women want to know whether they will be able to continue to care for their families, work, and pursue the activities they enjoy—that is, continue with their lives, despite treatment. Future research focusing on this aspect of patient care is needed.

Decisions about adjuvant chemotherapy are complex. No woman with localized breast cancer can know that she definitely will experience a recurrence in the absence of therapy, and even if she did, there is no guarantee that treatment will prevent such a recurrence. For that matter, even women with very early stage disease are at some risk of a systemic recurrence after local therapy alone. The potential benefits of adjuvant treatment need to be considered in conjunction with the risk of short-term and long-term side effects. Not only should the patient and physician consider the frequency and intensity of the side effects, but they must also consider how any particular side effect may impact an individual woman's life. Decisions about adjuvant treatment are often not clear-cut, but by weighing the advantages and disadvantages of a course of treatment, patients and their physicians can hope to make informed and thoughtful choices.

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Expert Opinion

Treatment of breast cancer during pregnancy

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The management of breast cancer during pregnancy is one of the great clinical challenges in oncology. Patients are best served by care provided through a multidisciplinary team, including surgeons, oncologists, obstetricians and genetics counsellors with experience in caring for similar women. The risks of diagnostic and therapeutic interventions can be mitigated by the consideration of known side effects of therapy on the fetus and mother. However, because of the limited amount of clinical experience available with such patients, the potential risks to the patient, the fetus and the pregnancy remain and are difficult to quantify. Treatment decisions need to be tailored carefully to the individual, respecting both her clinical circumstances and personal preferences.

Keywords: breast cancer, chemotherapy, pregnancy, side effects, tamoxifen

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1. Introduction

The treatment of breast cancer during pregnancy is a rare but challenging clinical problem. In principle, pregnant patients should receive treatment that is comparable to that of non-pregnant patients. Selecting the appropriate therapies is complicated by the important consideration of maternal and fetal health. Decisions must take into account several issues, including the patient's desire to continue the pregnancy, the clinical stage of the cancer, gestational age of the fetus, potential impact of treatment upon the patient's prognosis and long-term effects of therapy on the child and the patient. There is a growing amount of medical literature on the management of breast cancer in pregnancy, which can be valuable in helping patients and clinicians make treatment plans. However, it must be acknowledged that the available data to guide decisions regarding the management of breast cancer in pregnancy are derived from a small number of cases lacking long-term, comprehensive follow-up. Therefore, one cannot exclude small risks of jeopardy to the mother or the fetus and decisions are greatly influenced by the preferences of the patient and the best judgement of her clinicians.

1.1 Incidence and natural history

Breast and cervical cancers are the most common malignancies among women of childbearing age and the most common cancers diagnosed during pregnancy. The true incidence of breast cancer diagnosed during pregnancy is unknown. Historically, it has been estimated to represent between 0.2 – 3.8% of all known cases of breast cancer, affecting between 1 in 3000 – 1 in 10,000 pregnancies [1,2]. However, these estimates are derived from an old series of cases, mostly reported before 1980 and the widespread advent of screening mammography. It is probable that the concurrence of breast cancer and pregnancy represents a smaller proportion of all cases of breast cancer than had previously been observed, though the absolute number of such cases may be unchanged.

The diagnosis of breast cancer during pregnancy can be a clinical challenge. Physiological changes, including engorgement of the breast and vascular changes, can alter the sensitivity of physical examination at detecting breast tumours. A delay in

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breast cancer diagnosis during pregnancy may contribute to a later stage at presentation. Studies in the US, France and Japan have all demonstrated longer intervals between the first signs of breast cancer and diagnosis in women with pregnancy-associated breast cancer compared with non-pregnant breast cancer patients [3-5]. Thus, pregnant patients with unusual breast complaints or physical exam findings merit definitive evaluation of these symptoms.

Breast cancer during pregnancy was historically thought to confer a particularly grave prognosis. Retrospective studies at a variety of institutions demonstrate that women with breast cancer diagnosed during pregnancy have a high likelihood of axillary lymph node metastases. Estimates of nodal involvement range from 53 – 81% of cases, though in more modern series the likelihood of nodal involvement can be < 50% [6-8]. In contrast, most women diagnosed with non-pregnancy-associated breast cancer are likely to have node-negative disease. A delay in diagnosis probably plays a role in this stage progression for pregnant patients. Some studies have also suggested that cases of pregnancy-associated breast cancer are more likely to have other adverse prognostic factors, such as a lack of hormone receptor expression, overexpression of human epidermal growth factor receptor-2 or the presence of lymphatic and/or vascular invasion [9]. Furthermore, women diagnosed with breast cancer during pregnancy tend to be younger than non-pregnant breast cancer patients, who may carry an independent adverse prognosis.

While women with pregnancy-associated breast cancer may present with larger tumours and more advanced stage, the stage-adjusted prognosis for such patients appears to be similar to that for non-pregnant, age-matched women with breast cancer. Retrospective studies of women with pregnancy-associated breast cancer, matched for stage and age with appropriate non-pregnant controls, have suggested similar outcomes for both groups of patients [5,10-13]. Thus, assessment of prognosis for the pregnant patient relies upon the same clinical factors as for non-pregnant patients.

The historically poor prognosis for breast cancer during pregnancy led many clinicians to advocate therapeutic abortion. The actual benefits of therapeutic abortion are difficult to identify, owing to small numbers of cases in the literature identified over long-periods of time and without appropriate controls. In a series from the Mayo Clinic, women with more advanced disease were more likely to elect to have an abortion [8]. Such selection factors further complicate the understanding of the therapeutic effects of abortion. Abortion may be considered by the pregnant breast cancer patient for personal reasons, in order to simplify aspects of medical treatment and/or because of unavoidable damage to the fetus from radiation or chemotherapy. However, no available data suggests that abortion has therapeutic value for women with breast cancer [14].

1.2 Staging

Clinical staging of breast cancer relies upon assessment of tumour size, involvement of axillary lymph nodes and detection of metastatic disease. Among pregnant patients, the determination of clinical stage can be difficult, as physiological changes in breast tissue alter the clinical exam. Mammography is valuable in the routine evaluation of non-pregnant women with breast cancer to measure tumour size, assess for multifocal or multicentric lesions and screen the contralateral breast for a synchronous tumour. However, mammography in the pregnant patient may result in exposure of the fetus to ionising radiation. Shielding can minimise the potential radiation dose to the fetus. Ultrasonography can be safely used to evaluate the breast during pregnancy. If necessary to determine surgical options, magnetic resonance imaging (MRI) may also be employed to image the breasts in women with known lesions. It is not advised as a screening method for pregnant patients without clinical findings or known breast cancer.

Because pregnant patients do not receive surveillance mammography, most pregnant patients are diagnosed with breast cancer when a mass is palpated. The evaluation of a palpable mass is the same for a pregnant woman as for a non-pregnant woman. Ultrasound imaging with fine needle aspiration or core-needle biopsy can be done safely during pregnancy and is usually adequate to make a diagnosis. Milk fistula may complicate core-needle or excisional biopsy if performed after the thirty-sixth week of gestation when lactation changes occur in the breast [15,16]. Milk fistulae are generally managed with conservative measures and cessation of lactation when necessary.

Systemic staging for breast cancer typically relies on methods, such as bone scan or computed tomography, that expose patients to ionising radiation. For this reason, these studies are contraindicated in most pregnant patients, particularly when alternative imaging options are available. Staging chest x-rays with shielding have been safely used in pregnant women with breast cancer. Routine laboratory tests of bone marrow, hepatic and renal function should be done to monitor the patient. The serum alkaline phosphatase level may be elevated on account of pregnancy. Patients with focal symptoms can be evaluated with plain radiography imaging, provided that appropriate shielding is used [17]. Skeletal, brain or abdominal MRI can be used as needed to evaluate symptoms, though the absolute safety of gadolinium-enhanced MRI in pregnant women is not well characterised and ultrasound can be used to evaluate patients for hepatic metastases.

2. Local therapy

2.1 Surgery

Modified radical mastectomy or simple mastectomy with axillary node dissection remain the standard surgical techniques for pregnant women with breast cancer. For women who are near term, breast conserving surgery followed by radiation therapy to the breast after delivery may be an option. However, the effectiveness of radiation therapy at achieving local control has not been studied in patients diagnosed while pregnant or nursing. Sentinel lymph node mapping has not been studied among pregnant patients. Owing to changes in breast

physiology during pregnancy, the technique may be less reliable in pregnant or recently-pregnant patients. Furthermore, sentinel lymph node mapping typically requires the administration of radioactive tracers, another contraindication for the pregnant woman.

Surgery, including general anaesthesia, is considered safe in pregnant women. Although elective procedures may be delayed until later in pregnancy or postpartum, oncological surgeries should be scheduled expeditiously. There are case reports of miscarriage or preterm labour among women having surgical procedures for breast masses during pregnancy [18]. Pregnant patients undergoing anaesthesia with surgery are at risk for low birth weight deliveries, presumably a function of the underlying disorder necessitating surgery [19]. Women with breast cancer do not appear to have more perioperative complications than other pregnant women undergoing surgical procedures.

2.2 Radiation therapy

Radiation therapy is commonly offered to women with stage I – III breast cancer following breast surgery in order to prevent local-regional recurrence and improve survival. Radiation treatments administered with therapeutic intent carry much higher doses than diagnostic radiology studies and are therefore associated with greater risk to the fetus. Thus radiation therapy is contraindicated in pregnant patients [20]. Since mastectomy offers equivalent survival to lumpectomy followed by radiation, mastectomy is the surgery of choice in women with operable breast cancer diagnosed in early pregnancy.

The timing of radiation therapy and pregnancy may allow certain individuals to receive radiotherapy following delivery. In randomised clinical trials, delay of radiotherapy for up to six months to facilitate chemotherapy administration has not been shown to impair long-term survival [21]. Thus, radiation may be contemplated for some patients diagnosed with breast cancer in the second or third trimesters. Nonetheless, given the certainty of the utility of mastectomy and the uncertainty regarding delayed radiation, breast conservation in pregnant women and the need for definitive tumour control, mastectomy without radiation (or possibly with radiation after delivery) remains the preferred local treatment.

3. Systemic therapy

3.1 Tamoxifen

Tamoxifen is the standard of care for women with operable breast cancer and tumours that express hormone receptors, regardless of patient age [22]. The effects of tamoxifen (a partial oestrogen agonist and antagonist) on human pregnancy are unknown. There are theoretical and clinical reasons for believing the drug would have adverse consequences on pregnancy. In laboratory rodents, tamoxifen exposure during pregnancy is associated with intrauterine growth retardation [23]. *In utero* exposure to tamoxifen has been associated with urogenital abnormalities in neonatal laboratory animals [24,25] and humans [26] and may contribute to other congenital defects [27]. For these reasons, tamoxifen is contraindicated during pregnancy and nursing. Tamoxifen should be offered to women postpartum if their tumours expressed either the oestrogen- or progesterone-receptors.

3.2 Chemotherapy

Adjuvant chemotherapy is an important part of treatment for many women with early stage breast cancer [28]. Choosing chemotherapy is a difficult challenge for many patients with breast cancer as weighing the benefits and risks can prove daunting. Such considerations and/or decisions are even more difficult in the treatment of the pregnant patient. In most instances, very limited clinical experience and pharmacological data exist for assuring patients of the safety of treatments for themselves or for their offspring. For obvious reasons, the possible benefits of chemotherapy have not been formally studied in pregnant patients. It is likely that physiological changes in pregnancy alter the pharmacokinetics of chemotherapeutic agents, though it is not known if this effect is clinically significant. Because of these many unknown clinical factors, estimations of the benefits and risks of treatment are not easily done and patients and clinicians must make judgements tailored to their particular circumstances and preferences.

The effects of cytotoxic chemotherapy on pregnancy outcomes have been evaluated in hundreds of case reports and several comprehensive reviews. Most of these cases did not involve women being treated for breast cancer. Potential adverse effects of chemotherapy during pregnancy include miscarriage, teratogenesis, intrauterine growth retardation, premature birth and low birth weight [29-34]. Exposure during the first trimester, the time of active organogenesis, is particularly associated with increased risk of spontaneous abortion, fetal compromise and significant malformations in the child. To a surprising degree, exposure to chemotherapy in the second or third trimester is associated with a lower risk of teratogenic events or miscarriages. However, exposure during the second or third trimesters has been associated with some fetal anomalies and impaired birth weight [12,35]. Infants born shortly after chemotherapy exposure *in utero* may experience acute side effects of chemotherapy, including anaemia, neutropenia, thrombocytopenia and alopecia. These acute sequelae are generally transient and can usually be managed with appropriate anticipation and treatment.

Specific cytotoxic agents are associated with the more frequent adverse effects. Among agents utilised in treatment of breast cancer, the folic acid antagonist methotrexate has been associated with miscarriage and with a syndrome of complex congenital abnormalities. Fluorouracil may cause significant fetal abnormalities, as can alkylating agents such as cyclophosphamide, particularly when administered in the first trimester. Anthracycline exposure during the third trimester has been associated with fetal myocardial necrosis but not other abnormalities [36]. The side effects of taxane therapy on pregnancy or *in utero* development are unknown.

The longer term effects of chemotherapy exposure during pregnancy are not well characterised [37]. Small series of patients suggest that most children have overtly normal development following *in utero* exposure to chemotherapy. However, all such children should be followed for potential delayed effects, including cardiopulmonary, CNS or reproductive abnormalities.

In addition to considering the short- and long-term side effects of chemotherapy, special attention must be paid to supportive measures employed when treating pregnant patients [38]. Nausea and vomiting can be controlled with serotonin antagonists, such as ondansetron, which are also used to treat hyperemesis gravidarum. Metoclopromide and prochlorperazine may also be used, though these agents may affect prolactin levels and hence lactation. Corticosteroids may contribute to a variety of maternal and fetal complications. If needed, prednisone is the steroid of choice in pregnant patients, as it is metabolised before crossing the placenta. Pregnant patients merit close surveillance for dehydration or infection that may be aggravated by chemotherapy exposure. Because of the potential complications of bleeding and infection during labour, the timing of chemotherapy at the end of term is critical. If possible, chemotherapy should be withheld in the weeks prior to the anticipated due date to allow for hematological recovery.

In summary, chemotherapy can be administered to pregnant patients. In addition to the standard risks from cytotoxic treatment, chemotherapy poses particular risks to the developing fetus. The long-term consequences of fetal exposure to chemotherapy are not well known. Chemotherapy should be avoided during the first trimester, a time of critical embryogenesis and vulnerability. Thereafter, chemotherapy can be considered for appropriate patients with caution. It will never be possible to say that it is 'safe' to give chemotherapy to pregnant patients. However, it may be possible to gauge the risks and benefits adequately enough to suggest that such treatments are worthwhile.

4. A multidisciplinary approach to breast cancer in pregnancy

A recent publication from the MD Anderson Cancer Center in Houston, Texas reported on a series of 24 pregnant women with breast cancer, all treated according to a standardised protocol over an 8-year period [39]. As a prospective study, this report merits special attention for clinicians contemplating comprehensive treatment of the pregnant breast cancer patient. The guidelines used in the protocol developed at MD Anderson are appropriate for utilisation in treating such patients.

The pregnant patients with breast cancer in this series were managed by a multidisciplinary team of specialists (Box 1), including medical oncologists, surgeons, genetic counsellors and high-risk obstetricians. Patients signed informed consent that was specifically tailored to the risks – known and unknown – of treatment during pregnancy. All patients with operable disease were advised to have mastectomy with axillary node dissection; some patients received pre-operative chemotherapy. Staging studies were done to minimise risk to the fetus and to provide necessary clinical information. If appropriate, chemotherapy treatments were administered after the first trimester in a standardised fashion and fetal monitoring was also done according to a planned schedule.

Box 1. Multidisciplinary management of breast cancer in pregnant patients at MD Anderson

- Referral to maternal-fetal medicine specialist for accurate assessment of gestational age by ultrasonography
- Genetic counselling (offered) to discuss effect of chemotherapy on fetus
- Patients given option of terminating pregnancy or continuing pregnancy, with or without active treatment
- Surgical consultation for modified radical mastectomy with axillary node dissection
- Metastatic work-up including chest x-ray (with abdominal shielding), blood counts and renal and liver function tests
- Informed consent specifically tailored for treatment during pregnancy
- High-risk obstetrical care with serial fetal growth ultrasound every 3 or 4 weeks or as indicated and fetal nonstress test or biophysical profile between 28 weeks gestation and term
- Delivery as dictated by obstetrical indications
- Use of tocolytics and corticosteroids to treat preterm labour, up to 34 weeks gestation

A total of 24 patients formed the core of this study analysis. Of these, 22 had primary breast cancer and two had metastatic disease. Most patients had mastectomy but two patients had breast conserving surgery followed by postpartum radiation therapy and three patients with advanced disease did not receive any surgery. Patients received a median of four cycles of fluorouracil/doxorubicin/cyclophosphamide combination chemotherapy (Table 2). There were no unusual side effects reported. Preterm labour was experienced by 12% of patients and one patient (4%) had pre-eclampsia. Infants were delivered at a median gestational age of 38 weeks. Three infants were delivered before term, one because of pre-eclampsia and two because of preterm labour. Two women has postpartum endometritis. Because of chemotherapy exposure, women were instructed not to breast feed. Lactation was impaired in many women.

No congenital abnormalities were noted and only one child had birthweight < 10% for gestational age. Transient leukopenia was noted in one infant, one had hyaline membrane disease and two had alopecia. Normal Apgar scores were reported for all children. With median follow-up of 4 – 5 years, no abnormal childhood development issues were reported.

A retrospective survey of cancer centres in France has also analysed outcomes for women who received chemotherapy for

Table 2. FAC treatments for pregnant breast cancer patients at MD Anderson

- Chemotherapy (cycle every 21 – 28 days via central venous catheter)
- Cyclophosphamide 500 mg/m² iv. day 1
- Doxorubicin 50 mg/m² iv. by continuous infusion over 72 h
- Fluorouracil 500 mg/m² iv. days 1 & 4
- Supportive measures
- Complete blood counts and renal function tests, as needed
- Ondansetron and/or promethazine or prochlorperazine, as needed

FAC. Fluorouracil/doxorubicin/cyclophosphamide combination chemotherapy.

breast cancer during pregnancy [40]. In a nationwide survey, 20 patients were identified. A median of 2 cycles of chemotherapy were administered, typically starting in the third trimester. Roughly half the patients received fluorouracil/epirubicin/cyclophosphamide-based chemotherapy treatments. Two women who received chemotherapy in the first trimester had spontaneous miscarriages. One pregnancy treated with chemotherapy in the second trimester had intrauterine fetal demise. Four of 20 pregnancies had premature delivery (< 34 weeks). Based on the risk of preterm labour, the authors advise avoiding chemotherapy after the thirty-fifth week of gestation. Anaemia and leukopenia were noted in one infant each and two infants had respiratory distress at birth. One infant had intrauterine growth retardation and another infant died 8 days postpartum for reasons unknown. No infants had congenital anomalies. With median follow-up of 3 – 4 years, all surviving children reached normal developmental milestones.

These series offer some reassurance for treating pregnant patients with chemotherapy. They demonstrate that chemotherapy can be given to women with breast cancer in the second and third trimesters and that such therapy is manageable. They also highlight the potential dangers of such an approach.

5. Expert opinion

The treatment of breast cancer during pregnancy is an unusual but well defined oncological challenge. Physicians and patients must work together to make appropriate decisions for each patient. The principles of breast cancer management-optimal local and systemic control for long-term survival-are unchanged when treating pregnant patients. However, the timing and sequencing of therapy and the choice of specific regional and systemic treatments must take into account the unique circumstances of the pregnant breast cancer patient. Surgery, usually mastectomy with axillary node resection, is the mainstay of local therapy. Radiation therapy is contraindicated during pregnancy. Tamoxifen therapy is also contraindicated during pregnancy but should be offered to non-nursing patients with hormone-sensitive tumours after pregnancy. Systemic chemotherapy for breast cancer has been administered to pregnant women. The limited clinical experience available can be used to help doctors and patients make informed decisions on the appropriateness of chemotherapy during pregnancy.

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Expert Opinion on Pharmacotherapy

Article Type:	Review
Title :	Treatment of breast cancer during pregnancy
Authors:	HJ Burstein, AH Partridge & BA Lesnikoski
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Year:	2002
Abstract:	The management of breast cancer during pregnancy is one of the great clinical challenges in oncology. Patients are best served by care provided through a multidisciplinary team including surgeons, oncologists, obstetricians and genetics counsellors with experience in caring for similar women. The risks of diagnostic and therapeutic interventions can be mitigated by the consideration of known side effects of therapy on the fetus and the mother. However, because of the limited amount of clinical experience available, the potential risks to the patient, to the fetus and to the pregnancy are difficult to quantify. Treatment decisions need to be tailored carefully to the individual, respecting both her clinical circumstances and her personal preferences.
Keywords:	breast cancer, chemotherapy, pregnancy, side effects, tamoxifen

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Should patients with cancer be offered aggregate results of clinical trials in which they have participated?

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Patients with cancer are not routinely provided with results of trials in which they have participated, unless this information would influence their future care. We surveyed patients on a multicenter phase II clinical trial for first-line treatment of HER-2+ metastatic breast cancer regarding their attitudes about trial results. Methods: The survey, developed among patients enrolled in breast cancer clinical trials, was administered to patients enrolled on the trial for advanced breast cancer. Results: To date, 47 out of 51 consecutively enrolled patients (median age: 54 years, range 29-82) returned our voluntary survey, administered after the first treatment. 94% of respondents graduated high school; 57% graduated college; 87% were white. Almost all respondents (96%) wanted to be informed of the results, when the information becomes available, and 96% believed they have a "right" to be informed. 49% indicated their interest in the results might be influenced by how they respond to treatment. However, 87% of women believed they would want results even if they did not benefit from the therapy. College graduates were more likely (p=0.006) to want results regardless of their own clinical response; age did not predict such interest (p=0.14). If unable to be notified of results directly, 89% would want their family informed. Most patients (85%) indicated results should be provided by their physicians; 70% were willing to be contacted regarding results by mail. Conclusion: Participants in a trial for metastatic breast cancer indicated a preference for learning aggregate study results, and believed they have a right to such information. However, a patient's own response to treatment may affect her interest in results. Future studies should consider communication of results to interested participants and evaluate the impact of this information.

Appendix 5

Adolescent Diet and Incidence of Benign Breast Disease

Objective: Studies of adult diet and risk of breast cancer have yielded inconsistent results, but this does not rule out the possible impact of childhood and adolescent diet. This study examined associations between components of adolescent diet and incidence of benign breast disease (BBD), which may be a precursor marker of breast cancer.

Methods: The study population consisted of 29,378 women in the Nurses' Health Study II who completed a questionnaire on adolescent diet. Between 1991 and 1997, 4994 of these women reported a first diagnosis of BBD, and 997 of these cases (20%) were reported as biopsy-confirmed. Valid tissue samples were obtained for 753 cases of biopsy-confirmed BBD. Incidence rate ratios and 95% confidence intervals (CI) for self-reported BBD and histologically-confirmed BBD were calculated for quartiles of energy-adjusted fat and nutrient intakes.

Results: We observed no consistent associations between incidence of self-reported BBD or histologically-confirmed BBD and intake of total fat or any subtypes of fat during adolescence. Fiber and vitamin E intake during adolescence were inversely associated with incidence of self-reported BBD and proliferative BBD. Compared to women in the lowest quartile of vitamin E intake, the age-adjusted rate ratios for proliferative BBD were 0.92 (95% CI: 0.72-1.17) for women in the second quartile, 0.82 (95% CI: 0.63-1.06) for women in the third quartile, and 0.72 (95% CI: 0.55-0.94) for women in the highest quartile (p for trend = 0.01). Compared to women in the lowest quartile of fiber intake, the age-adjusted incidence rate ratios for proliferative BBD were 0.96 (95% CI: 0.75-1.22) for women in the second quartile, 0.92 (95% CI: 0.72-1.18) for women in the third quartile, and 0.68 (95% CI: 0.52-0.89) for women in the highest quartile (p for trend = 0.01). Further adjustment for age at menarche, body mass index at age 18, family history of breast cancer, and alcohol intake did not substantially change the incidence rate ratios.

Conclusions: Fiber and vitamin E intake during adolescence may be inversely associated with risk of BBD. Confirmation of these associations may offer a means for prevention of breast cancer if BBD is a plausible precursor marker of breast cancer development.

Heather Baer